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Allergen immunotherapy for allergic asthma: a systematic review and meta-analysis

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Abstract

Background: To inform the development of the European Academy of Allergy and Clinical Immunonology's (EAACI) Guidelines on Allergen Immunotherapy (AIT) for allergic asthma, we assessed the evidence on the effectiveness, cost-effectiveness and safety of AIT.

Methods: We performed a systematic review, which involved searching nine databases. Studies were screened against pre-defined eligibility criteria and critically appraised using established instruments. Data were synthesized using random-effects meta-analyses.

Results: 98 studies satisfied the inclusion criteria. Short-term symptom scores were reduced with a standardized mean difference (SMD) of -1.11 (95%CI -1.66, -0.56). This was robust to a pre-specified sensitivity analyses, but there was evidence suggestive of publication bias. Short-term medication scores were reduced SMD -1.21 (95%CI -1.87, -0.54), again with evidence of potential publication bias. There was no reduction in short-term combined medication and symptom scores SMD 0.17 (95%CI -0.23, 0.58), but one study showed a beneficial long-term effect.

For secondary outcomes subcutaneous immunotherapy (SCIT) improved quality of life and decreased allergen specific airways hyperreactivity (AHR) but this was not the case for sub-lingual immunotherapy (SLIT). There were no consistent effects on asthma control, exacerbations, lung function, and non-specific AHR.

AIT resulted in a modest increased risk of adverse events (AEs). Although relatively uncommon, systemic AEs were more frequent with SCIT; however no fatalities were reported.

The limited evidence on cost-effectiveness was mainly available for sublingual immunotherapy (SLIT) and this suggested that SLIT is likely to be cost-effective.

Conclusions: AIT can achieve substantial reductions in short-term symptom and medication scores in allergic asthma. It was however associated with a modest increased risk of systemic and local AEs. More data are needed in relation to secondary outcomes, longer-term effectiveness and cost-effectiveness.

Keywords: allergy, allergen immunotherapy, asthma, cost-effectiveness, desensitization, effectiveness, exacerbations, lung function, quality of life, safety.

BACKGROUND

Asthma is a major public health problem affecting over 300 million people worldwide.(1) Its prevalence and impact are particularly on the rise and it is estimated that by 2025 an additional 100 million people may develop asthma.(2) Asthma is therefore set to become one of the world's most prevalent chronic diseases.

Based on the clinical history, examination and investigative procedures, different asthma phenotypes have been described.(3) The pathogenesis of asthma is extremely complex and several disease endotypes have been suggested.(3,4) Allergic asthma is one of best described asthma phenotypesof primary studies. Allergic sensitization is a strong risk factor for asthma inception and severity in children and in adults.(5)

Current asthma therapies can effectively control symptoms and the ongoing inflammatory process but do not affect the underlying, dysregulated immune response. Thus, they are very limited in controlling the progression of the disease. Allergen immunotherapy (AIT) is the only etiology-based treatment for allergic diseases capable of disease modification, as demonstrated by prevention of both the onset of new allergic sensitizations and disease progression.

The European Academy of Allergy and Clinical Immunology (EAACI) is in the process of developing *Guidelines on Allergen Immunotherapy (AIT) for Allergic Asthma*. We undertook a systematic review of primary studies on the effectiveness, cost-effectiveness and safety of AIT for allergic asthma in order to inform the formulation of key clinical recommendations.

METHODS

A detailed outline of the methods have previously been published in the protocol of this review.(6) We therefore confine ourseleves to a synopsis of the methods employed.

A highly sensitive search strategy was developed, and validated study design filters were applied to retrieve articles pertaining to the use of AIT for allergic asthma from electronic bibliographic databases. The search strategy was developed on OVID MEDLINE and then adapted for the other databases (see Appendix 1, Supplementary file). In all cases, the databases were searched from inception to October 31, 2015. Additional papers were located through searching the references cited by the identified studies, and unpublished work and research in progress was identified through discussion with experts in the field. There were no language restrictions employed.

Inclusion and exclusion criteria are detailed in Box 1

Patient characteristics	Studies conducted on patients of any age with a physician confirmed diagnosis of asthma, plus evidence of clinically relevant allergic sensitization as assessed by an objective biomarker (e.g., skin prick test or specific-IgE), in combination with a history of asthma symptoms due to allergen exposure
Interventions of interest	AIT for different allergens (e.g. pollens, house dust mites (HDM), animal dander, cockroach and molds), administered through either subcutaneous (SCIT) or sublingual (SLIT) routes.
Comparator	Placebo or any active comparator.
Study designs	*Effectiveness:* Double-blind randomized controlled trials (RCTs). Originally, we planned to include data from any RCT, irrespective of whether there was blinding. This was changed due to the large volume of RCT studies. This decision was made prior to any analyses being undertaken. *Cost-effectiveness:* Health economic analysis. *Safety:* Double-blind RCTs and large case series (≥300 patients).
Outcomes	*Primary outcomes:* Effectiveness, both short-term (i.e. during treatment) and long-term (i.e. at least a year after discontinuation of AIT) as assessed by symptom and/or medication scores. *Secondary outcomes:* Asthma control; asthma specific quality of life (QoL); exacerbations; lung function; response to environmental exposure chamber or bronchial allergen challenge; health economic analysis from the perspective of the health system/payer; and safety as assessed by local and systemic reactions.(7,8)
Exclusion criteria	Reviews, discussion papers, non-research letters and editorials, animal studies and studies not employing double-blind RCT designs.

Box 1. Inclusion and exclusion criteria

Study selection

All references were uploaded into the systematic review software DistillerSR and underwent de-duplication. Studies were independently checked by two reviewers (SD, FA or AK) against the above inclusion criteria. Any discrepancies were resolved through discussion and, when necessary, a third reviewer was consulted (AS).

Quality assessment

Quality assessments were independently carried out on each study by two reviewers (FA, AK, DD, SD or MK). We used the Cochrane Risk of Bias (ROB) tool to assess RCTs,(9) the Critical Appraisal Skills Programme (CASP) Economic Evaluation Checklist for health economic studies,(10) and the National Institute for Health and Clinical Excellence (NICE) quality assessment tool to critically appraise case series.(11) Any discrepancies were resolved by discussion or arbitration by a third reviewer (AS).

Data extraction, analysis and synthesis

Data were independently extracted onto a customized data extraction sheet in DistillerSR by two reviewers (FA, AK, HZ, DD or SD) and any discrepancies were resolved by discussion or arbitration by a third reviewer (AS). A descriptive report with summary data tables was produced to summarize the literature. Where clinically and statistically appropriate, meta-analyses were undertaken using random-effects modeling.(12) Where standardized mean difference (SMD)has been used the scale used is 0.2 represents a small effect size, 0.5 a medium effect size and 0.8 a large effect size. (105)

Sensitivity and assessment for publication bias

Sensitivity analyses were, where possible, undertaken by comparing the summary estimates obtained by excluding studies judged to be at high ROB with those judged to be at low or moderate ROB.

Where possible, publication bias was assessed through the creation of funnel plots, and tested by Begg's rank correlation test and Egger's regression test.(13,14)

Subgroup analyses

A number of sub-group analyses were undertaken,details of which are in the protocol.

Registration and reporting

This review has been registered with the International Prospective Register of Systematic Reviews (PROSPERO): CRD42016035372. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist was used to guide the reporting of the systematic review (Appendix 2, Supplementary file).

RESULTS

Our search strategy yielded 7,490 papers of which 98 studies were eligible; these comprised of 89 double-blind RCTs (reported in 94 papers), three cost-effectiveness studies and six case series (see Figure 1).

Effectiveness

Description of studies

The RCTs enrolled a total of 7,413 patients. The route of administration of AIT was SCIT (n=54), SLIT (n=34), and SCIT versus SLIT (n=1). The majority of trials reported on the short-term effectiveness of AIT with only one SLIT trial reporting on long-term effectiveness. The 54 SCIT trials (reported in 57 papers) included 2,305 patients.(15–70) and the 34 SLIT trials (71–104)(reported in 36 papers) included 5,108 patients. SCIT studies included adults (n=24), both children and adults (n=17), and children (n=13). SLIT studies included children (n=20), both children and adults (n=10), and adults (n=4). Allergen extracts administered included HDM, grass, cat, dog, trees, molds, latex and weeds. Various AIT protocols were utilized. The severity of asthma tended to be mild-to-moderate. Further details are included in Tables 1a, 1b, 1c and S1a, S1b, S1c (Supplementary file).

Quality assessment

The majority of SCIT trials (n=32) were judged as unclear ROB, seven low ROB and 15 studies as at high ROB (Table S1d, Supplementary file). Twenty SLIT studies were assessed to be at high ROB; 13 studies were at unclear ROB; and one study at low ROB (Table S1e, Supplementary file). The one SCIT vs SLIT study was judged to be at a low ROB (Table S1f, Supplementary file).

Primary outcomes

Symptom scores

Short-term

Fifty-eight (36 SCIT and 22 SLIT) trials reported on the effect of symptoms at the end of the AIT treatment period. We were able to pool data from 15 SCIT and SLIT trials with placebo as comparator. The metaanalysis showed that AIT improved symptom scores with a standardized mean difference (SMD) of -1.11 (95%CI -1.66, -0.56) (Figure 2), these suggesting a large effect of AIT.(105)

Sensitivity analysis

By excluding studies at high ROB sensitivity analysis confirmed the effect of AIT on asthma symptom scores: SMD -1.44 (95%CI -2.14, -0.74) (Figure S2a, Supplementary file).

Publication bias

The funnel plot showed possible publication bias as evidenced by an excess of small studies with large effect sizes (Figures S2b, Supplementary file). Publication bias was also suggested by the Egger test (P=0.024). There were insufficient studies to undertake the Begg test

Subgroup analyses

- Children (<18 years) versus adults (≥18 years): SMD -0.58 (95%CI -1.17, -0.01) in children and SMD -1.95 (95%CI -3.28, -0.62)) in adults (Figure 3), supporting AIT effectiveness in both children and adults.
- SCIT versus SLIT: the analyses found that SCIT is effective with SMD -1.64 (95%CI -2.51, -0.78) and suggested (but did not confirm) that SLIT was effective SMD -0.35 (95%CI -0.75, 0.05) (Figure 4); this indirect comparison suggested that SCIT was more effective than SLIT.
- Treatment duration: SMD -1.15 (95%CI -1.77, -0.53) in those treated for <3 years and SMD -0.79 (95%CI -1.10, -0.49) in those treated for ≥3 years (Figure S2c, Supplementary file), these analyses finding that both treatment durations were effective.
- Mild/moderate versus moderate/severe disease: this subgroup analyses found that AIT is effective for mild/moderate asthma SMD -1.00 (95%CI -1.81, -0.19) and suggested (but did not confirm) a possible benefit in those with moderate/severe disease SMD -0.23 (95%CI -0.89, 0.43) (Figure S2d, Supplementary file)
- Individual allergens: this subgroup analyses found evidence of benefit for AIT with HDM SMD -1.41 (95%CI -2.27, -0.55), grass pollen SMD -1.18 (95%CI -2.17, -0.20) and cat/dog dander (SMD -0.77 (95%CI -1.48, -0.06)), suggested (but did not confirm) benefit for tree pollen SMD -0.24 (95%CI -0.91, 0.42), and found no benefit for mold SMD 0.36 (95%CI -0.39, 1.11). (Figure S2e, Supplementary file)
- Monosensitized/mono-allergic versus polysensitized: there is evidence of AIT benefit in monosensitized/mono-allergic patients SMD -4.23 (95%CI -5.53, -2.94) and a suggested benefit

(but not confirmed) for polysensitized patients SMD -0.31 (95%CI -0.65, 0.04) (Figure S2f, Supplementary file),

Long-term

No studies reported on the long-term effectiveness of AIT on symptom score.

Medication scores

Short-term

Forty-two (28 SCIT and 14 SLIT) studies reported on medication scores.. Pooling of data with placebo as the comparator was possible for 10 studies. Meta-analysis found evidence that AIT improved medication scores (i.e. reduced medication use) with a SMD of -1.21 (95%CI -1.87, -0.54) (Figure 5), this corresponding to a large effect.

Sensitivity analysis

Sensitivity analysis for this outcome was not possible as no studies were found to be at high ROB.

Publication bias

The funnel plot showed possible publication bias as evidenced by an excess of small studies with large effect sizes (Figures S2g, Supplementary file), but this was not confirmed by the Egger test (P=0.09). There were insufficient studies to undertake the Begg test.

Subgroup analyses

- Children (<18 years) versus adults (≥18 years): there is evidence for benefit in children SMD -0.49 (95%CI -0.98, 0.00) and a suggested benefit (but not confirmed) in adults SMD -4.45 (95%CI -11.23, 2.32) (Figure 6)
- SCIT versus SLIT: SMD -1.65 (95%CI -2.52, -0.79) for SCIT and SMD -0.29 (95%CI -0.82, 0.24) for SLIT (Figure 7), these analyses showing benefit of SCIT and suggesting (but not confirming) benefit from SLIT.
- Mild/moderate versus moderate/severe disease: SMD -1.59 (95%CI -2.48, -0.70) for mild/moderate disease and SMD -0.36 (95%CI -1.03, 0.31) (Figure S2h, Supplementary file),

these analyses showing a benefit in those with mild/moderate disease and suggesting (but not confirming) benefit in those with moderate/severe disease.

- Treatment duration: SMD -1.21 (95%CI -1.94, -0.49) for those treated for <3 years andSMD -1.29 (95%CI -2.00, -0.59) for those receiving ≥3 years of treatment (Figure S2i, Supplementary file), these analyses showing evidence of benefit in both groups.
- Individual allergens: this subgroup analysis demonstrated a benefit of AIT with HDM (SMD -2.10 (95%CI -3.29, -0.91) and tree pollen (one study) (SMD -1.08 (95%CI -1.79, -0.37)) and suggested (but not confirmed) a benefit for, grass pollen (SMD -0.06 (95%CI -0.41, 0.28)) and molds (SMD -0.65 (95%CI -1.92, 0.62) (Figure S2j, Supplementary file).
- Monosensitized and mono-allergic versus polysensitized: SMD -1.18 (95%CI -1.16, 0.13) in mono-sensitized and mono-allergic and the polysensitized group (SMD -0.36 (95%CI -2.11, 0.25)) in the polysensitized group (Figure S2k) these analyses suggesting (but not confirming) benefit in both groups.

Long-term

No studies reported on the long-term effectiveness of AIT on medication score.

Combined symptom and medication scores

Short-term

Six studies (two SCIT, three SLIT studies and one SCIT vs. SLIT) reported a combined assessment of the effectiveness of AIT on symptoms and medication usage. Pooling of data was possible for two studies, this showing a SMD of 0.17 (95%CI -0.23, 0.58) (Figure 8).

Sensitivity analysis, assessment of publication bias and subgroup analyses

These analyses were not possible for this outcome.

Long-term

One SLIT study at low ROB reported on this outcome. A five-year double blind placebo RCT by Durham (2012) had a three year SLIT tablets or placebo treatment period in grass pollen allergic patients followed by a two-year blinded observation period when no active treatment was administered. At the

end of the five years the group who had received SLIT were found to have a significant improvement in combined asthma symptom and medication scores when compared to placebo for the whole five-year period (p=0.049).

Secondary outcomes

Asthma control

Seven SLIT studies reported on a measure of asthma control (see Table S1g for details). (77,78,85,88,93,98,100). We were unable to pool data due to the differences in reporting of results. The one study at low ROB found that AIT did not improve asthma control(98) . We found no evidence to assess whether SCIT is effective in improving asthma control in allergic asthma patients.

Quality of life

Eleven AIT trials reported on a measure of disease-specific QoL (Table S1h).

Three SCIT studies (19,35,106), all judged to be at low ROB, reported significant improvements in disease-specific QoL. Pooled data from two of these trials (19,35), showed a large treatment effect with an SMD of -0.83 (95%CI -1.19, -0.47) in favor of SCIT (Figure 9).

Seven SLIT trials reported on disease-specific QoL (77,78,83,88,93,98,100). We were unable to pool data from these studies for meta-analysis due to the variable reporting of results (Table 2). The one low ROB trial of SLIT(98) showed no significant improvement in disease-specific QoL.

Exacerbations

Six trials (69,78,80,88,91,98) reported on asthma exacerbations, which were defined in a number of ways (Table S1i). The one SCIT trial at low ROB (69) reported on exacerbations defined by the number of courses of oral corticosteroids required to restore asthma control found no significant difference between the SCIT and placebo groups (P-value not given). Five SLIT studies reported on exacerbations, which we were unable to pool due to variations in the ways in which trial results were reported.

In summary, focusing on the trials at low ROB, the Wang (2006) SCIT trial failed to demonstrate evidence of a reduction in exacerbations in those treated with AIT compared with those treated with placebo. Two SLIT trials reported a positive effect of AIT on asthma exacerbations, one in the context of reducing the dose of ICS.

Lung function

Twenty-five studies, of variable quality, reported on measures of lung function: peak expiratory flow rate (PEF), forced expiratory volume in 1 second (FEV1) and forced expiratory flow at 25–75% of forced vital capacity (FEF 25-75%). Data on these outcomes were recorded in a number of ways and at varying times throughout the study.

Peak expiratory flow rate (PEF)

Fourteen studies reported on this outcome.(16,29,38,43,48,50,61,69,72,73,93,96,107,108) (Table S1j). Pooled data from six studies suggested no clear benefit of AIT with a SMD of 0.48 (95%CI -0.21, 1.18) (Figure S4a)

Forced expiratory volume (FEV1)

Nine studies reported on FEV1. Reporting of data was varied (18,28,43,57,73,93,96,108,109) (Table S1k). Data pooled from two studies indicated no clear evidence of benefit associated with AIT with a SMD of 0.41 (95%CI -0.46, 1.27) (Figure S4a)

Forced expiratory flow at 25–75% of forced vital capacity (FEF25-75)

We were able to pool data on FEF 25-75 from three trials (72,96,109) and found an SMD of 0.83 (95%CI 0.31, 1.35), this suggesting a large beneficial effect of AIT (Figure S4a).

In summary, the evidence identified from meta-analysis evaluating the effect of AIT on lung function in allergic asthma supports the effectiveness of AIT on small airways (FEF 25-75%), but with no clear evidence of benefit on improving PEF or FEV1.

Bronchial provocation tests

Thirty-one trials reported on bronchial provocation tests. Twenty-one trials looked at allergen specific provocation tests and 18 studies evaluated non-specific measures of bronchial hyperreactivity. There was a wide variation in reporting of outcome data (Tables S1l and S1m).

Allergen specific airway hyperreactivity

Twenty-one trials performed allergen specific bronchial provocation tests (15,17–20,25,30,31,35,44,48,53,60,62,64,67,70,82,107,108,110). They were of variable quality and were mainly SCIT trials (n=20), SLIT being evaluated in only one trial (82). (Table S1l).

Pooled data from three SCIT studies, demonstrated a large effect of AIT with a SMD of 0.93 (95%CI 0.08, 1.79) (Figure S4b). Furthermore, there was evidence from eight high quality RCTs that SCIT was effective in reducing allergen specific bronchial reactivity in patients with allergic asthma

One SLIT study reported on allergen specific bronchial responsiveness to Artemisia pollen (Leng 1990). This study, at moderate ROB, found no significant difference between the SLIT and placebo groups.

Non- specific airway hyperreactivity

Eighteen studies reported on this outcome (16–18,20,33,36,48,55,62,67,69,72,73,94,96,106,109,110) (Table S1m).

Pooling of data was possible for metacholine PC20 for three studies which showed an SMD of 0.74 (95%CI -0.17, 1.66) , showing no clear evidence of benefit for AIT; Histamine PC20 for two studies with an SMD of 0.33 (95% CI 0.03, 0.64) favouring AIT and for metacholine PD20 for two studies showing an SMD of 0.03 (95%CI -0.32, 0.39) showing no clear evidence in favour of AIT (Figure S4c). We were able to combine data from seven of these studies which showed an overall SMD of 0.33 (95%CI 0.01, 0.64) in favour of AIT (Figure S4d)

Cost-effectiveness

One SCIT and two SLIT studies satisfied the eligibility criteria. (111–113) These included children and adults with or without allergic rhinitis (Tables S1m and S1n). The quality appraisal is detailed in Tables S1o and S1p.

Of the three studies included only one focused on patients with allergic asthma who did not also have allergic rhinitis.(111) This study was carried out in Germany and compared SCIT with standard care based on a small scale RCT (N=65) with three years of follow-up data. The study used a disease specific outcome measure (i.e. mean morning peak flow) with no attempt to convert it to a general quality of life measure such as quality adjusted life years (QALYs) making it impossible to assess the cost-effectiveness of the treatment. The study found that, over the three years, SCIT was more expensive than standard care and performed better than standard care on the disease specific outcome measure.

The remaining two studies looked at patients with both asthma and allergic rhinitis. SLIT was compared with standard care in an RCT (N=151) with one year of follow-up conducted in Austria, Denmark, Germany, Holland, Italy, Spain, Sweden and the UK, and with results evaluated from an English National Health Service (NHS) perspective.(112) This study used one year of treatment data and assumed a constant treatment effect over the three year treatment period and the six years following the end of the treatment. EQ5D was used to evaluate the treatment outcome. The incremental cost-effectiveness ratio (ICER) of SLIT, as compared to standard care at 2005 prices, was calculated at £8816 (€10850) per QALY over the nine year period. The study did not attempt to characterize the uncertainty around this estimate. Updating this to 2014/15 prices using Personal Social Services Resource Unit (PSSRU) NHS inflation indices gave an ICER of £10726 (€13202) per QALY. Another RCT (N=70) with five years of follow-up conducted in Italy comparing SLIT with standard care in patients with asthma and rhinitis and found that patients on SLIT cost less and experienced less symptoms than those on standard care.(113) Methods for calculationg the costs were not presented in enough detail to understand the analysis that had been performed and there was no attempt to convert the symptom score to a general quality of life scale making it impossible to assess the cost-effectiveness of SLIT.

Safety

Data from randomized controlled trials (RCTs) and case series were included to assess the safety of AIT.

RCTs

Fifty-two RCTs (36 SCIT studies and 16 SLIT) reported safety data (Tables S3a-f). We were able to pool data from 38 of these studies (SCIT=29;SLIT=9) including both local and systemic adverse events (AEs)

Risk of patients experiencing one or more AE

AIT delivered by any route (SCIT or SLIT) increased the risk of patients experiencing one or more AE (i.e. local and systemic) with a rate ratio (RR) of 1.74 (95%CI 1.38, 2.2) (Figure S3a). Subgroup analysis found that the increased risk was higher for SCIT RR=2.22 (95% CI 1.48, 3.33) than SLIT RR=1.49 (95%CI 1.13, 1.98), although this is an indirect comparison.(Figures S3b and S3c)

Total number of AEs reported

AIT delivered by any route (SCIT or SLIT) increased the risk of total AEs (i.e. local and/or systemic) with a RR=1.50 (95%CI 1.12, 2.02) (Figure S3d). Subgroup analysis found increased risk both for SCIT(RR=1.32 (95%CI 1.01, 1.74) and SLIT (RR=1.93 (95%CI 0.95, 3.95) . (Figures S3e and S3f).

Risk of systemic AEs

AIT delivered by any route (SCIT or SLIT) increased the risk of systemic AEs with a RR of 1.85 (95%CI 1.20, 2.84) (Figure S3g). Subgroup analysis found that there was clearly an increased risk of systemic AEs with SCIT RR=1.92 (95%CI 1.19, 3.09), but not for SLIT RR=1.39 (95%CI 0.67, 2.92) (Figures S3h and S3i)

Risk of local AEs

AIT delivered by any route was not found to increase the risk of local AEs: RR=1.18 (95%CI 0.83, 1.67) (Figure S3j). The available data suggested that the risk of local AEs was however substantially greater in those receiving SLIT when compared to those receiving SCIT (Figure S3j).

Case-series

We identified six eligible case-series studies in our searches; SCIT (n=5)and SLIT (n=1). The main characteristics of these studies and quality appraisal are presented in Tables S3g and S3h. The reported incidence of local AEs varied from 0.66 per patient and 0.33 per injection to 1.8% The reported incidence of systemic AEs varied from 0.0074% to 0.06%

No deaths from AIT were reported in any of these studies.

DISCUSSION

Statement of principal findings

This review has found a substantial body of evidence showing that administration of AIT in patients with allergic asthma can result in reductions in short-term symptom and medication scores. These findings do however need to be interpreted with caution given that the majority of trials were found to be at high or unclear ROB and the possibility of publication bias in relation to both these outcomes. Further sub-group analysis confirmed the beneficial effect for SCIT but was questionable for SLIT. There was a more modest body of evidence for the combined symptom and medication scores, which meta-analysis suggested was ineffective but this was not conclusively demonstrated on account of the wide confidence intervals. We found only one trial, judged to be at low ROB, evaluating long-term outcomes, which found a significant improvement in combined symptom and medication scores.

There is evidence for SCIT in improving asthma specific quality-of-life and reducing allergen specific airway hyperreactivity. In terms of lung function we were unable to demonstrate any significant beneficial effect on PEFR and FEV1 however SCIT does have a beneficial effect on FEV25-75. No beneficial effect of AIT could be demonstrated on asthma control. As for asthma exacerbations, no beneficial effect could be demonstrated for SCIT, but there was limited evidence in favour of SLIT.

AIT was associated with a moderate increased risk of AEs, both for SCIT and SLIT. Severe systemic AEs were observed, but these were uncommon and mainly occurred with SCIT. No fatalities were reported in the studies included in this review.

Strengths and limitations

To our knowledge, this is the most comprehensive assessment of AIT in asthma ever undertaken. We employed internationally accepted techniques to systematically identify, assess and synthesize a substantial body of evidence, which included a number of pre-specified sensitivity and subgroup analyses.

The limitations of this review need to be considered. First, despite our extensive searches we may not have uncovered all relevant evidence on this subject. Second, we were limited by the heterogeneity in approaches used to assess outcomes, which meant we were unable to pool data from all trials or undertake all the planned subgroup analyses. The results of this review, particularly for primary outcomes, are based on the trials which we were able to meta-analyse which may not be representative of all trials. For example, data for combined scores was only available for six studies of which only two could be pooled for meta-analysis the results of which had a wide confidence interval allowing no clear conclusion to be drawn. For the subgroup analyses that were undertaken, there was in some cases imprecision which impacted on our ability to draw clear conclusions. Third, because of the heterogeneity in scoring systems used, we undertook meta-analyses using random-effects modeling and pooled data using SMDs, which can be difficult to interpret. The absolute size of the SMD was used to guide assessment of the likely effect size demonstrated. Finally, it needs to be borne in mind that there may have been important differences between specific AIT products. Investigating this issue was however beyond the scope of this review.

Interpretaion in the light of the previous literature

The findings from this review are in keeping with earlier evidence syntheses on this subject (see companion paper), which found that SCIT inproved short-term symptom amd medication scores and measures of bronchial reactivity, but the evidence for SLIT was less consistent. There was no clear improvement of lung function for either SCIT or SLIT. This present study has built on this body of

work by adding a broader range of subgroup analyses, including additional studies at low ROB, and achieveing greater precision in summary results.

Implications for policy, practice and research

Our findings provide evidence that AIT may be effective in improving two of our three patient-reported primary outcomes over the short-term. Interpretation of these results is however complicated by considerations about the quality of the substantial number of studies and possible publication bias. The subgroup analyses suggest that SCIT is likely to be more effective than SLIT, and that AIT may be more effective in children than in adults

Greater standardization of trial designs, looking at the compliance of patients to AIT for the differing routes of administration, reporting and choice of outcomes and their reporting so as to facilitate evidence syntheses and key subgroup analyses would greatly help to advance the body of evidence underpinning AIT in allergic asthma. Future well conducted studies looking at the combined symptom and medication score are needed to determine whether AIT is beneficial for this outcome. We hope that future researchers will build on the findings from this systematic review and aim to fill key evidence gaps and areas of continuing uncertainty.

The findings from this review will be used to inform the development of recommendations for EAACI's Guidelines on AIT. We anticipate that this review will report mid 2017.

Conclusions

There is evidence that AIT in allergic asthma can achieve substantial reductions in short-term symptom and medication scores, with subgroup analyses confirming a benefit from SCIT and a questionable benefit from SLIT. These findings however need to be interpreted with caution given concerns about study quality and potential publication bias. Further there is evidence showing that SCIT decreases allergen-specific airway hypereactivity and improves asthma specific quality-of-life. The effect of AIT on asthma control and exacerbations is not conclusive, neither its long-term efficacy after stopping AIT, which requires further investigation. More research is needed to establish the cost-effectiveness of AIT but evidence suggest that SLIT is cost-effective in a UK NHS environment.

AIT is associated with a modest increase in the risk of AEs, both for SCIT and SLIT. Severe systemic AEs can occur, but are uncommon and mainly associated with SCIT. No fatalities were reported in the studies included in this review.

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Additional material:

Figures and tables for main paper

Appendix 1: Search strategy

Appendix 2: PRISMA Checklist

S1: Supplementary tables

S2: Supplementary figures for primary outcomes

S3: Safety tables and figures

S4: Supplementary figures for secondary outcomes

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Allergen immunotherapy for allergic asthma: a systematic review and meta-analysis

Figures and tables for main paper

Table 1a: Overview of SCIT trials (n=54 studies in 57 papers)

Study Author, year, country	Allergen(s) type								Allergen no.		Comparator			AIT Protocol										Short-term effectiveness			Long-term effectiveness			Safety	Quality of life	Lung function	Corticosteroid use	Asthma exacerbations	Bronchial tests
	Grass pollen(s)	Tree pollen(s)	Weed(s)	Mould(s)	HDM	Cat	Dog	Other (s)	Single	Multiple	Placebo	Routine care	Active	Pre-seasonal	Co-seasonal	Continuous	Conventional	Cluster	Semi-rush	Rush	Ultra-rush	Rx duration	Product type/Name (manufacture)	Symptom score	Medication score	Combined score	Symptom score	Medication score	Combined score						
Aas, 1971, Norway					X				X		X						X					3 y	Two house dust extracts from Nyegaard et Co., Oslo (house dust group A), and from Allergologisk Laboratorium, Copenhagen (House dust B), respectively.											X	X
Adkinson, 1997, US	X	X		X	X			X		X	X						X					2 y	SCIT mixture of seven aeroallergens(HDM ragweed, grass mix, Bermuda grass, white oak, Alternaria, cladosporium, aspergillus) prepared by ALK Laboratories, Copenhagen, Denmark, vs placebo	X	X					X		X	X		X
Alvarez-Cuesta, 1994, Spain						X			X		X						X					1 y	The allergen extract was obtained from Alergia e Inmunologia (Abell6, S.A., Madrid, Spain) and prepared by extracting the raw material (cat dander supplied by Allergon AB Engelholm, Valinge, Sweden)	X	X					X			X	X
Alvarez, 2002, Spain					X				X		X											1y	D. pteronyssinus D. pteronyssinus extract at 10											

																							biological units / mL contained 4µg/mL of Der p1 and 2 µg/mL of Der p2, entrapped in liposomes vs placebo									X			X
Ameal, 2005, Spain					X				X		X						X					1 y	The active group received a modified allergen extract of D. pteronyssinus. The modified extract was adsorbed onto aluminium hydroxide.	X	X					X	X			X	X
Armentia-Medina, 1995, Spain								X	X		X						X					1 y	Standardised extract of storage mite Lepidoglyphus destructor with an activity of 100BU/ml. Concentration 18%	X										X	X
Arvidsson, 2004, Sweden		X							X		X											1 y	Standardized birch pollen extract (Alutard SQ Betula verrucosa; ALK-Abello) vs dilute histamine dihydrochloride.									X		X	X
Basomba, 2002, Spain					X				X		X						X					1 y	D pteronyssinus encapsulated in liposomes containing 0.025, 0.05, 0.1, 0.2, 0.4, 0.8, 1.6, and 3.2 µg of Der p 1.	X	X					X				X	X
Blumberga, 2006, Denmark					X				X		X						X					3 y	Subcutaneous SIT with Alutard SQ D.							X			X		
Bødtger, 2002, Denmark		X							X		X							X				1 y	High dose birch pollen extract, commercially available and produced by ALK-Abello, Hørsholm, Denmark. The content of the major birch pollen allergen Bet v 1 was 12 mg/100 000 SQ-U.	x	x					x					
Bousquet, 1985, France					X				X		X									X		7 w	Standardized Dermatophagoides pteronyssinus extract							x		X		X	X
Bousquet, 1990, France	X								X		X		X							X		1 y	High and low dose grass extract.	X						X					

Cantani, 1996 Italy	X			X	X	X	X			X	X											3m	Mixture of grass, other pollen, mould, house dust mite and cat and dog dander	X	X									X
Chakraborty, 2006, India		X							X		X						X					2 y	P sylvestris pollen extract standardized with one of its principal allergenic fraction	X	X					X		X		
Creticos, 1996, US			X						X		X						X					2 y	Lyophilized extract of short ragweed pollen (Greer Laboratories, Lenoir, N.C.)	X	X					X				
Dolz, 1996, Spain	X								X		X									X		3 y	The grass-pollen allergen extract Alutard SQ. aluminium hydroxide-adsorbed allergens PDL (Phleum, Dactylis, Lolium), was used.											X
Dreborg, 1986, Sweden & Finland				X					X		X							X				10 m	Purified and standardised Cladosporium herbarum allergen preparation.	X	X					X				X
D'Souza, 1973, UK					X				X		X						X					3 m	The D. pteronyssinus extract was prepared by Beecham Research Laboratories.	X	X					X				
Franco, 1995, Italy					X				X		X						X					15 m	Alum absorbed Alpare D pteronyssinus extract	X	X					X			X	X
Gaddie, 1976, UK					X				X		X						X					1 y	Tyrosine-adsorbed depot form of D pteroniyssinus vaccine (Migen, Bencard)	X	X					X		X		
Garcia-Robaina, 2006, Spain					X				X		X						X					54 w	The active group received a mixture of modified allergen extracts containing 50% D pteronyssinus and 50% D farinae	X	X					X		X	X	X

Haugaard, 1992, Denmark						X	X			X	X						X					5 m	Extracts used for diagnosis and treatment were Pharmalgen® cat epithelium extract and dog dander extract (Pharmacia AB, Uppsala, Sweden. AEK, Hersholm, Denmark).							X		X		X		X
Hedlin, 1999, Denmark	X	X			X	X				X	X		X				X					3 y	Partly purified and standardized extracts of cat dander, Dermatophagoides pteronyssinus, timothy pollen, and birch pollen were provided by ALK (Hørsholm, Denmark).							X		X			X
Hui, 2014, China					X						X	X					X					3 y	The SCIT treatment was initiated at a dosage of 20 U/ml, and was continued weekly with an increase in the dosage each week	X						X		X	X		
Kuna, 1989, Poland	X								X		X						X					1 y	Glutaraldehyde-modified, tyrosine-adsorbed grass pollen (Pollinex, Bencard Allergy Service, Brentford, Middlesex, England).	X						X					
Kuna, 2011, Poland				X					X		X											3 y	Standardized A alternata extract (Novo-Helisen Depot, A alternata 100%; Allergopharma Joachim Ganzer KG, Reinbek, Germany) in a depot formulation with aluminium hydroxide	X	X					X	X				
Lewis, 1971 UK					X				X				X		X							6-9 months	HDM D. farinae 0.002% to 0-1% w/v	X									X		
Leynadier, 2000, Germany								X	X		X									X		1 y	Standardized latex extract (Stallergènes)	X											

Maestrelli, 2004, Italy					X				X		X						X					4 y	A 1:1 mixture of D pteronyssinus and D farina extracts adsorbed to aluminium hydroxide in normal saline solution (ALKAbello, Madrid, Spain)	X	X							X			
Malling, 1986, Sweden				X					X		X							X				1 y	Lyophilized, partially purified and biologically standardized preparation of Cladosporium herbarum (Pharmalgen®, Pharmacia, Uppsala, Sweden)												X
Malling, 1987, Sweden 2nd paper original study 1986				X					X		X							X				1 y	Lyophilised, partially purified and biologically standardised preparation of Cladosporium herbarum (Pharmalgen, Pharmacia, Uppsala, Sweden) was used.												
Marques, 1978, Italy					X				X		X						X					14 m	Six syringes numbered in order of dose, each containing 0.5 ml of D pteronyssinus extract absorbed into tyrosine	X						X					
Mosbech, 1989, Denmark					X				X				X				X					2 y	Biologically standardized and purified unmodified Dp extract (Pharmalgen). The mPEG-modified Dp extract was produced by coupling activated mPEG-succinate to the un-modified Dp extract. A buffered solution of isotonic saline containing 0.3 mg/ml albumin, 0.4% phenol, and phosphate 0.95 mg/ml was used for mPEG-modified extract.	X	X										
Mosbech, 1990, Denmark					X				X				X									2 y	Single batch of unmodified, purified Dp-extract (Pharmalgen) biologically standardized was used. By RAST-inhibition, 10-11,000 BU of this extract equated 100,000 SQ-U of a similar mite allergen extract (Aquagen, ALK, Horsholm, Denmark). Part of this							X					

																							batch was modified with mPEG (3,000 Daltons). The unmodified extract was reconstituted in a diluent containing aluminiumhydroxide, whereas no such additive was present in the buffered saline used for the mPEG-modified extract.													
Newton, 1979, UK					X				X		X											15 m	Alum-precipitated D. farinae									X			
Ohman, 1984, US						X			X		X						X					3 m	Active-treatment vials reconstituted in 50% glycerine to a concentration of 13units of cat allergen 1 per millilitre							X		X		X	X
Olsen, 1997, Denmark					X				X		X						X					1 y	Active treatment with extracts of either Dermatophagoides pterotryssinus (Dpt) or D. farinae (Dfa) (Alutard® SQ, ALK, Denmark).	X	X					X		X			X
Ortolani, 1984, Italy	X								X		X						X					6 m	Aqueous lyophilized extract (Hollister-Stier, Spokane, Washington) of 89 velvet, 1/3 sweet vernal, and 89 timothy grass pollen	X											
Pauli, 1984, (not stated. Authors from France & UK)					X				X		X						X					1 y	Dpt tyrosine- adsorbed extract	X	X										
Pene, 1998 France						X			X		X											6 weeks	Fel d 1 peptides												X
Price, 1984, UK					X				X		X						X					2 y	Tyrosine glutaraldehyde modified D. pteronyssinus antigen, "Migen', Bencard.		X										

Rak, 2001, Sweden		X							X		X		X				X						Standardized depot preparations of birch pollen allergen extract (Alutard SQ, ALKAbelló) containing water-soluble allergen extract and aluminium hydroxide	X	X									X	X
Reid, 1986, US	X								X				X				X					8 m	Seven grass mix in serum, plus other allergens specific to individuals	X	X					X					
Roberts, 2006, UK	X								X		X							X				2 y	Alutard SQ P pratense (ALK-Abello) was used. This is an alum-adsorbed preparation of pollen from P pratense with a recommended dose of 100,000 SQ-U.	X	X					X		X	X		
Sabbah, 1991, France					X				X		X						X					180 d	Alpha-Fraction-Retard-D. pteronyssinus	X	X					X					
Smith, 1971, UK					X				X				X				X						HDM extract	X	X					X					
Sundlin, 1986, Sweden						X	X			X	X						X					18 m	Partially purified, standardized allergenic extracts of cat or dog dander							X				X	X
Tabar, 2008, Spain				X					X		X						X					1 y	Metabolic extract of A. alternata that had been biologically standardised	X	X					X		X			
Taylor, 1978, US						X			X		X						X					4 m	1.6 mg/ml cat allergen							X		X			

Taylor, 1978, UK					X				X		X						X					10 w	HDM fortified house dust vaccine							X		X			
Valovirta, 1984, Finland							X		X		X						X					1 y	Commercial standardised aluminium hydroxide bound dog dander extract (Alutard SQ)											X	X
Valovirta, 1986, Finland 2nd paper original study 1984							X		X		X						X					1 y	Commercial standardised aluminium hydroxide bound dog dander extract (Alutard SQ)	X						X					
Van Bever, 1992, Belgium					X				X		X								X			1 y	Aqueous extract of Dermatophagoides pteronyssinus (10 BU·ml 1)	X								X			X
Van Metre, 1988, US						X			X		X						X					2 y	Cat allergenic extract ALK 1209/229452 was supplied by Allergologisk Laboratories, Copenhagen, Denmark							X		X		X	X
Vidal, 2011, Spain					X				X		X											4 m	D. pteronyssinus extract with the major allergens Der p 1 and 2		X					X			X		
Wang 2006 China					X				X		X											52w	Dermatophagoides pteronyssinus extract	X	X					X		X	X		X
Warner, 1978 UK					X				X		X											1 year	D. pteronyssinus absorbed into tyrosine ('Migen', Bencard).	X	X					X			X		X

***AIT**, allergen specific immunotherapy; **d,** day; **HDM**, house dust mite; **m,** month; **NR**, not reported; **SCIT**,* subcutaneous immunotherapy; ***SLIT**, sublingual immunotherapy; **w**, week; **y**, year*

Table 1b: Overview of SLIT trials (n=34 studies in 36 papers)

Study Author, year, country	Allergen(s) type								Allergen number		Comparator			AIT Protocol										Short-term effectiveness			Long-term effectiveness			Safety	Quality of life	Lung function	Corticosteroid use	Asthma exacerbations	Bronchial
	Grass pollen(s)	Tree pollen(s)	Weed(s)	Mould(s)	HDM	Cat	Dog	Other(s)	Single	Multiple	Placebo	Routine care	Active	Pre-seasonal	Co-seasonal	Continuous	Conventional	Cluster	Semi-rush	Rush	Ultra-rush	Rx duration	Product type/ Name (manufacture)	Symptom score	Medication score	Combined score	Symptom score	Medication score	Combined score						
Alvarez-Cuesta, 2007, Spain						X			X		X						X					1 y	Aqueous solution of standardized semi-purified cat dander extract	**X**	X	X									
Bachelier, 2001, Turkey					X				X		X						X					26 w	Dermatophagoide(D.pteronyssinus)+Dermatophagoidesfarinea (D. farinea) 50/50 extract	X	X					X		X	X		X
Bousquet, 1999, France					X				X		X						X					108 w.	HDM SLIT	X	X	X				X	X	X	X		X
Caffarelli, 2000, Italy	X								X		X						X					13 w and 9 week follow up post treatment	Grass pollen tablet (33% Holcus lanatus, 33% Phleum pratense and 33% Poa pratensis)	X	X	X				X					
Cao, 2007, China					X				X		X						X					3 m	Dermatophagoides Farinae Drops		X					X		X	X		

Dahl, 2006, Denmark & Sweden	X								X		X			X	X		X					19.5 w	Timothy grass (Phleumpratense) GRAZAX tablet 75,000 SQ-T once daily	X	X										
de Blay, 2014, Denmark, Germany, Italy, Spain, UK, Sweden, France & Poland					X				X		X		X				X					1 y	Oral lyophilisates containing standardized extracts of D pteronyssinus and D farinae in a 1:1 ratio. One development unit corresponds to 1 SQ-HDM			X				X	X	X	X		
Devillier, 2015, China					X				X		X						X					"52 w (+ 12 week baseline period before randomisation)"	HDM SLIT (D. pteronyssinus and D. farinae), approximately 28 mcg Der P 1 and 50mcg Der f 1 daily (300 IR)							X	X	X		X	
Drachenberg, 2001, Germany	X								X		X						X					6 m	Standardized allergen extract (ORALVAC birch n = 21 resp. grass/rye = 28)			X					X				
Durham, 2012	X								X		X			X	X		X					5y(3 Rx, 2 follow up)	Timothy grass (Phleumpratense) GRAZAX tablet 75,000 SQ-T once daily						x						
Gomez Vera et al, 2005, Mexico					X				X		X						X					6 m	Dermatophagoides pteronyssinus 1 standardized allergens (IPI-ASAC, Mexico) at a total dose of 10,469 UBE		X					X		X		X	
Ippoliti, 2003, Italy						X			X		X						X					26 w (with 3-month run-in)	HDM SLIT (D. pteronyssinus), maintenance dose 5 drops of 10 BU/mL 3 times a week	X								X			

Leng, 1990, unclear country			X					X	X		X						x					7.14 w (13 w post-treatment follow-up)	Artemisia pollen SLIT daily up-dosing to a maximum of 16416 PNU. Cumulative dose 396,652.06 PNU							X					X
Lewith, 2002, UK					X				X		X										X	16 w.	Homeopathic HDM SLIT administered on 3 occasions over 24 hours. Dose 30 dilutions of 1:100								X	X				
Lue, 2006, Taiwan					X				X		X						X					24 w (2 eeks post-treatment follow-up)	HDM SLIT daily with 3 week initiation phase. Maximum 20 drop dose of 300 IR/mL. Cumulative dose of 41,824 IR	X	X							X			
Ma, 2010, China					X				X			X	X				X					1 y	SLIT immunotherapy with Der F drops	X						X		X	X		
Ma, 2014, China					X				X		X						X					1 y	SLIT immunotherapy with Der F drops		X					X					
Moreno-Ancillo, 2007, Spain	X							X		X	X						X					248 d	biologically standardized by major allergens and quantified in micrograms, without up-dosing	X	X	X									
Mosbech, 2014, Denmark, Germany, Italy, Spain, UK, Sweden, France & Poland					X				X		X		X				X					52 w (1 y treatment duration)	Orallyophilisates containing standardized extracts of Dpteronyssinus and D farinae in a 1:1 ratio. Three active strengths were investigated: 1, 3, and 6 SQ-HDM. The units were designated in development units. One development unit corresponds to 1 SQ-HDM.	X						X	X	X	X	X	
Mosges et al, 2010, Germany	X								X		X										X	9 m	Standardized birch pollen (Betula alba) allergen extract. Ultra-rush high-dose SLIT titration regimen							X					

																							reaching the maintenance dose of 300 IR within 90 min (30–90–150–300 IR)									X			
Niu, 2006, Taiwan					X				X		X		X									24 w (+2 week off-treatment follow up)	HDM SLIT (D. Pteronyssinus and D. farinae), incremental dosing up to maintenance dose (cumulative dose ~ 41824 IR, which was equivalent to 1.7 mg D.p. and 3.0 mg D.f.)	X	X					X		X			
Pajno, 2000, Italy					X				X		X		X									104 w	HDM SLIT (D. pteronyssinus), incremental dosing schedule followed by maintenance 2.4 mg Der P 1 and 1.2 mg Der P 2 per week (in 3 doses/wk)		X	X				X				X	
Pajno, 2002, Italy									X		X		X									56 w (with 52 week off-treatment follow-up)	Parietaria pollen SLIT (Parietariajudaica), incremental dosing schedule followed by maintenance twice/wk (cumulative Par j ~ 20.3 mcg)	X	X									
Pajno, 2004, Italy			X					X	X		X						X					56 w (with 52 week off-treatment follow-up)	Parietaria pollen SLIT (Parietaria judaica), incremental dosing schedule followed by maintenance twice/wk (cumulative Par j ~ 20.3 mcg)									X			X

Pham-Thi, 2007, France					X				X		X						X					78 w.	HDM SLIT (D. Pteronyssinus and D.farinae), up-dosing for 2 w up to 300 IR concentration once daily (average cumulative dose was 155,000 IR, corresponding to 6.9 mg Der P 1 and 14.7 mg Der f 1)	X	X					X	X	X	X		
Reilly, 1994, UK				X	X			X	X		X						X					4 w (with 4 w 'optional' post-treatment follow-up)	Homeopathic SLIT (allergen varied, decided on case-by-case basis; HDM (84.6% of participants); feathers (7.7%); mixed moulds (7.7%)). 3 doses in 24 hours then optionally repeated at 4 w (according to patient choice)			X						X			X
Reinert, 1983, Germany	X								X		X						X					2 y	Troponholistersteir			X								
Stelmach, 2009, Poland	X								X		X										X	104 w.	Grass pollen SLIT (Dactylisglomerata, Anthoxanthumodoratum, Loliumperenne, Poapratensis, Phleum pretense). Ultra-rush period(total of 24 0IR). At the beginning of the next day, every morning before breakfast, received 4 puffs (120 IR) for 6 m. Cumulative dose 43,800 IR	X	X					X		X			X
Tian, 2014, China					X				X		X						X					48 w.	HDM SLIT (D. farinæ), titrated up over the first 4 w to 333 mcg/mL once daily	X										

Virchow, 2016, Germany					X				X		X												20 m (11 August 2011 to 24 April 2013)	HDM SLIT tablet contains extract from 2 species of cultivated HDM (D pteronyssinus and D farinae), produced in a standardized process with a 1:1:1:1 ratio of the major allergens (Group1 allergens of D farinae and D pteronyssinus and Group2 allergens of D farinae and D pteronyssinus), and formulated as rapidly dissolving oral lyophilisate for sublingual administration (ALK).	X						X				X	
Vourdas, 1998, Greece		X							X		X												104 w (2 y)	Olive pollen SLIT, daily up-dosing then each morning pre- and co-seasonally from January to July for 2 y up to a maximum of 20 drops of 300 IR (total 30,000 IR/y)	X	X					X		X			
Wang, 2014, China		X							X		X												52 w (+12 w baseline period before randomisation)	HDM SLIT (D.pteronyssinus and D. farinae), approximately 28 mcg Der P 1 and 50 mcg Der f 1 daily (300 IR)	X	X					X	X	X	X		
Wood, 201, US & UK								X	X		X			X		X							13 w.	Greer German cockroach extract							X					

Zhang, 2013, China					X				X			X										36 m	Standard dermatophagoides farinae drops (1~4) usage:1~3 were for increasing period of treatment for 3w, 1 times a day.												
Zhang, 2015, China					X				X			X										36 m	Dermatophagoides farina drop (1drop/time and 1 time/day)												
Zheng et al, 2012, China					X				X			X										36 months	Standard dermatophagoides farinae drops												

***AIT**, allergen specific immunotherapy; **d,** day; **HDM**, house dust mite; **m,** month; **NR**, not reported; **SCIT**,* subcutaneous immunotherapy; ***SLIT**, sublingual immunotherapy; **w**, week; **y**, year*

Table 1c: Overview of SCIT vs SLIT trials (n=1)

Study Author, year, country	Allergen(s) type								Allergen no.		Comparator			AIT Protocol										Short-term effectiveness			Long-term effectiveness			Safety	Quality of life	Lung function	Corticosteroid use	Asthma exacerbations	Bronchial tests
	Grass pollen(s)	Tree pollen(s)	Weed(s)	Mould(s)	HDM	Cat	Dog	Other (s)	Single	Multiple	Placebo	Routine care	Active	Pre-seasonal	Co-seasonal	Continuous	Conventional	Cluster	Semi-rush	Rush	Ultra-rush	Rx duration	Product type/Name (manufacture)	Symptom score	Medication score	Combined score	Symptom score	Medication score	Combined score						
Yukselen,2012, Turkey					X				X		X		X				X						HDM (D. pteronyssinus and D. farinae) (50/50) for sublingual and subcutaneous administration.	**X**	X					X		X			

Figure 1: PRISMA diagram

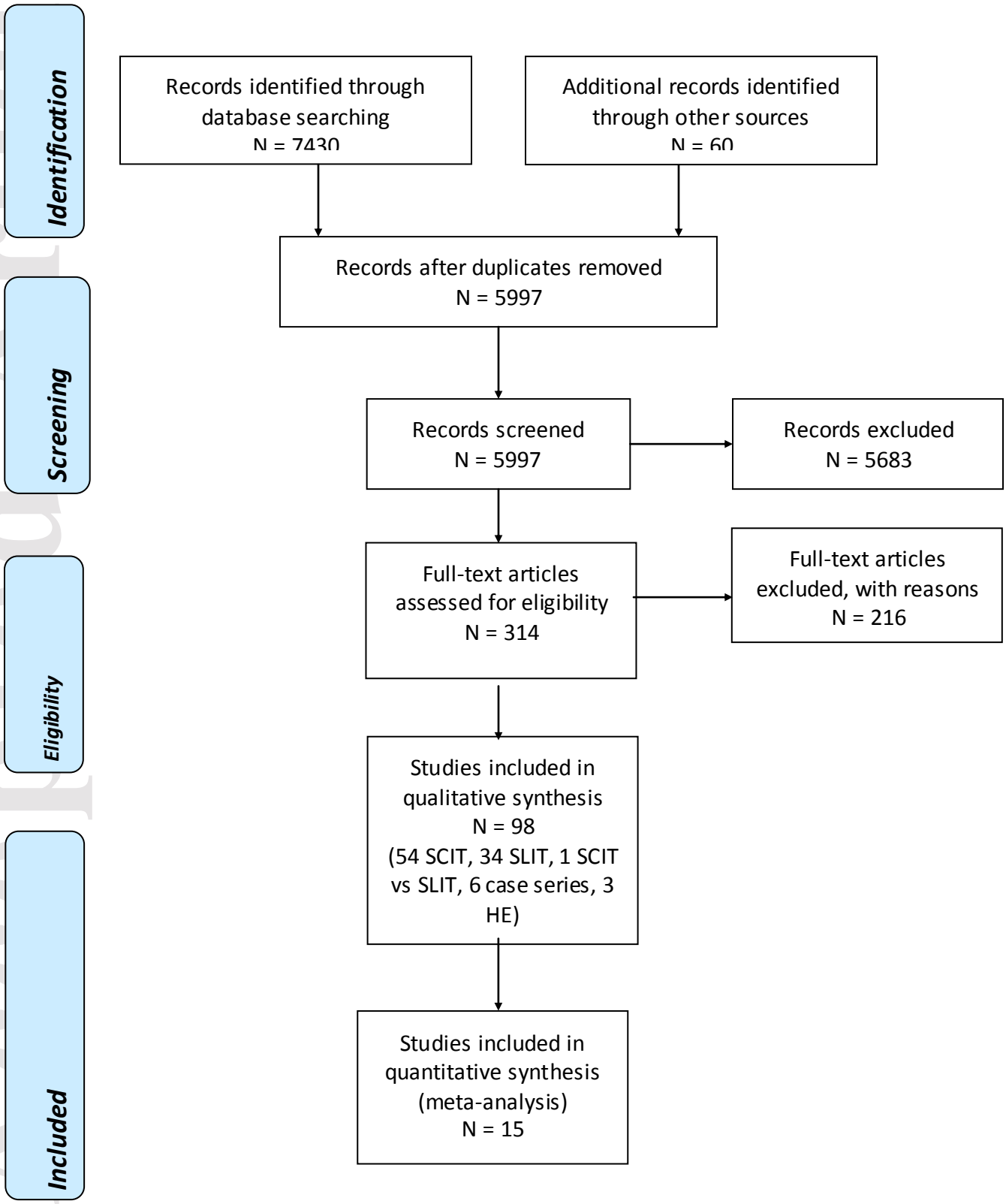
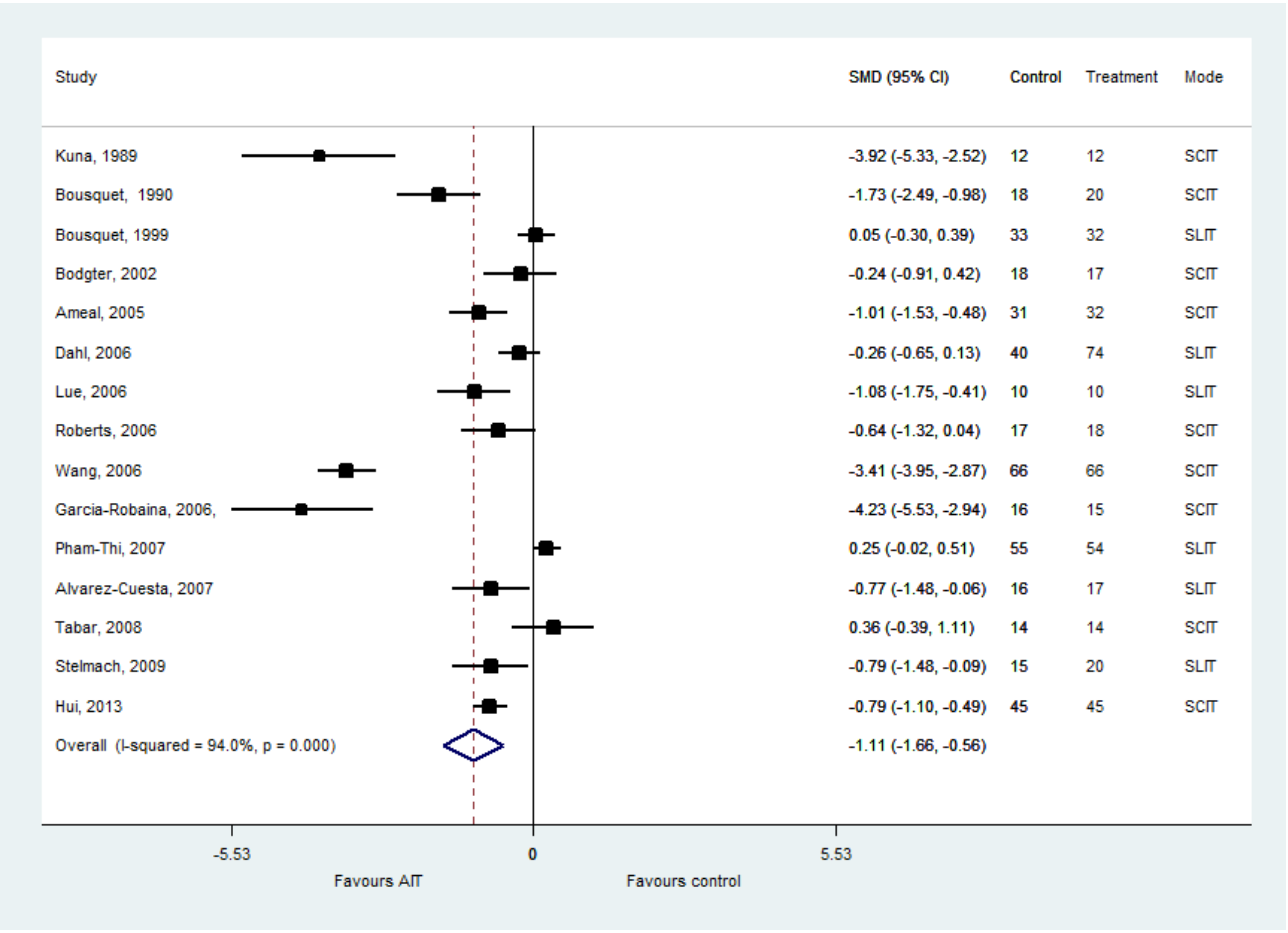
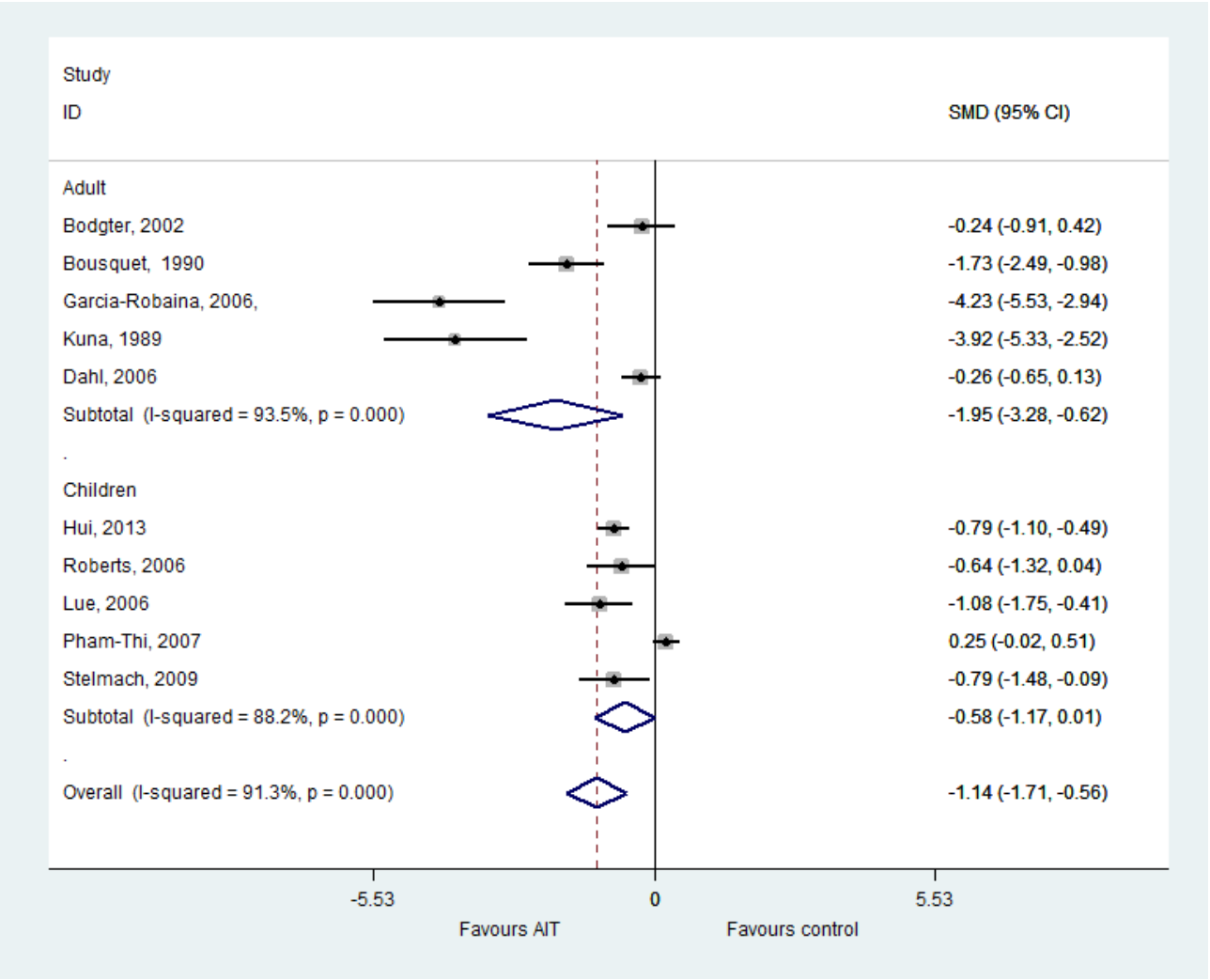


Figure 2: Meta-analysis of double-blind RCTs for symptom scores comparing AIT (SLIT and SCIT) and placebo groups (random effects model)



Test of ES=0: z= 3.96 p = 0.000
Heterogeneity chi-squared = 234.28 (d.f. = 14) p = 0.000
I-squared (variation in ES attributable to heterogeneity) = 94.0%
Estimate of between-study variance Tau-squared = 1.0488

Figure 3: Meta-analysis of double-blind RCTs, comparing symptom scores between AIT (SLIT and SCIT) and placebo groups in children <18 versus adults ≥18 years(random effects model)



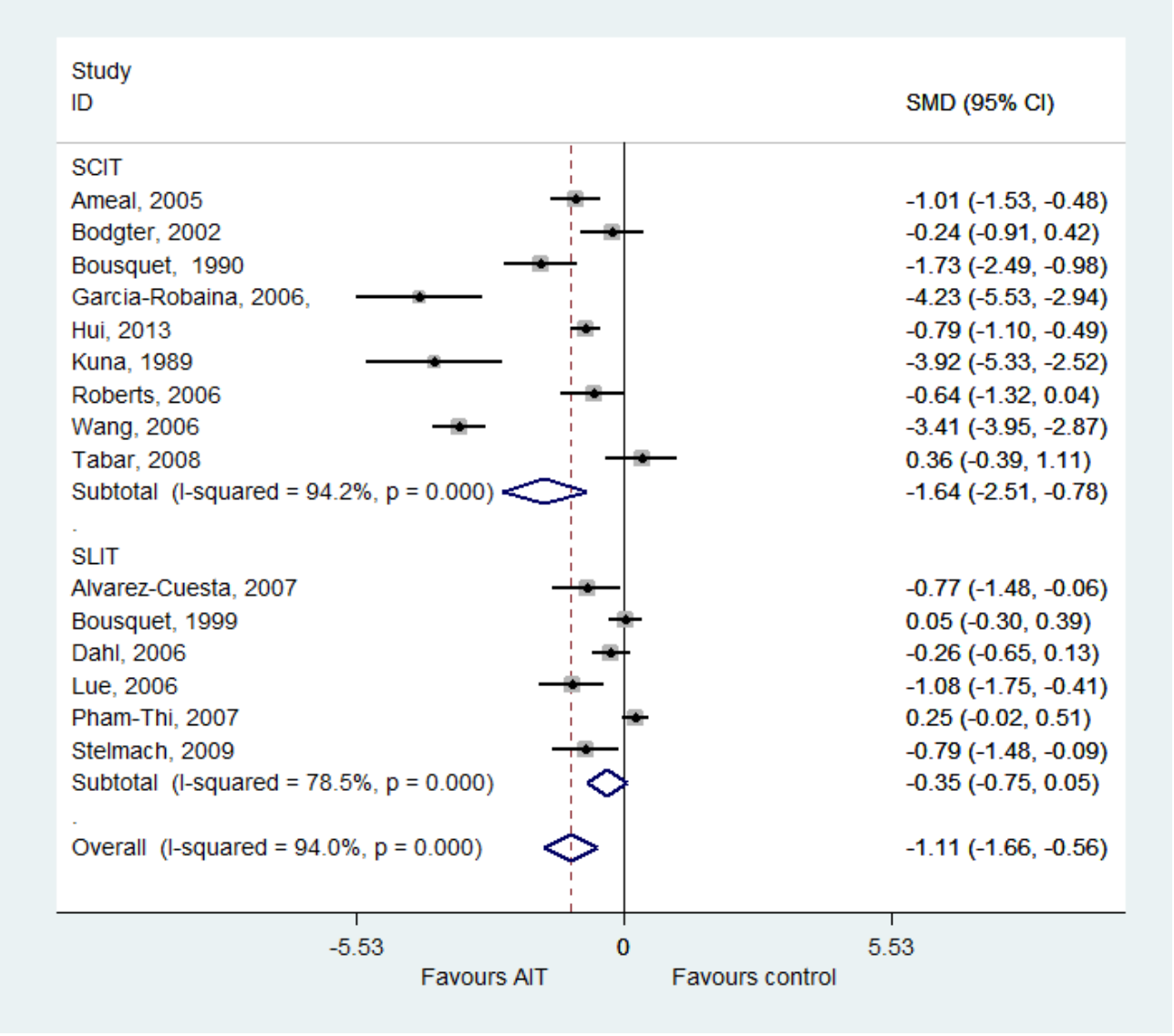
Test(s) of heterogeneity:

	Heterogeneity Statistic	degrees of freedom	P	Isquared**	Tau-squared
Adult	61.83	4	0.000	93.5%	2.0670
Children	34.02	4	0.000	88.2%	0.3750
Overall	104.04	9	0.000	91.3%	0.7215

Significance test(s) of ES=0

Adult	z= 2.87	p = 0.004
Children	z= 1.93	p = 0.054
Overall	z= 3.87	p = 0.000

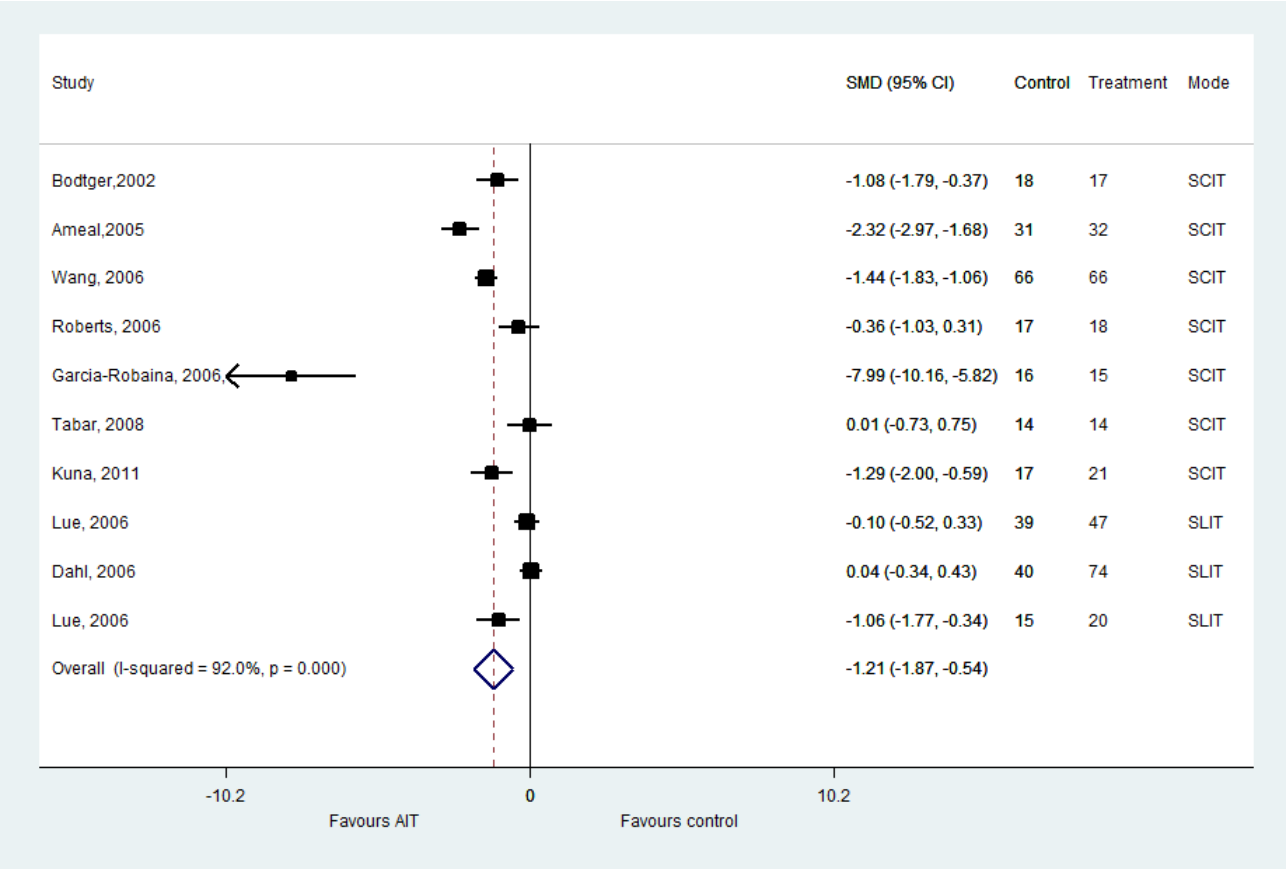
Figure 4: Meta-analysis of double-blind RCTs, comparing symptom scores between SCIT versus SLIT (random effects model)



	Heterogeneity Statistic	degrees of freedom	P	Isquared**	Tau-squared
SCIT	137.11	8	0.000	94.2%	1.5937
SLIT	23.26	5	0.000	78.5%	0.1810
Overall	234.28	14	0.000	94.0%	1.0488

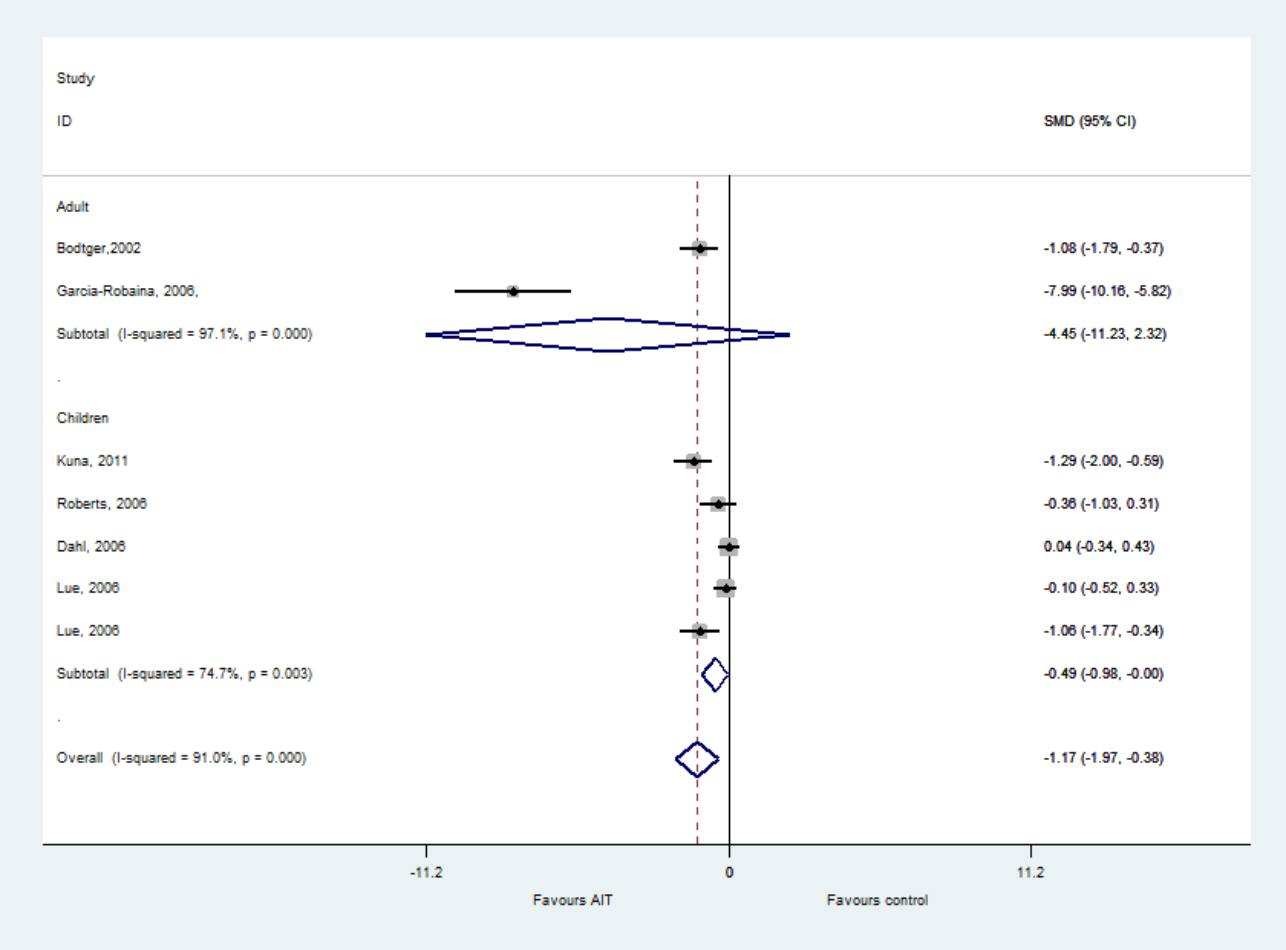
SCIT	z= 3.71	p = 0.000
SLIT	z= 1.71	p = 0.087
Overall	z= 3.96	p = 0.000

Figure 5: Meta-analysis of double-blind RCTs, comparing medication scores between AIT (SLIT and SCIT) and placebo groups (random effects model)



Test of ES=0 : z= 3.56 p = 0.000
Heterogeneity chi-squared = 112.48 (d.f. = 9) p = 0.000
I-squared (variation in ES attributable to heterogeneity) = 92.0%
Estimate of between-study variance Tau-squared = 0.9967

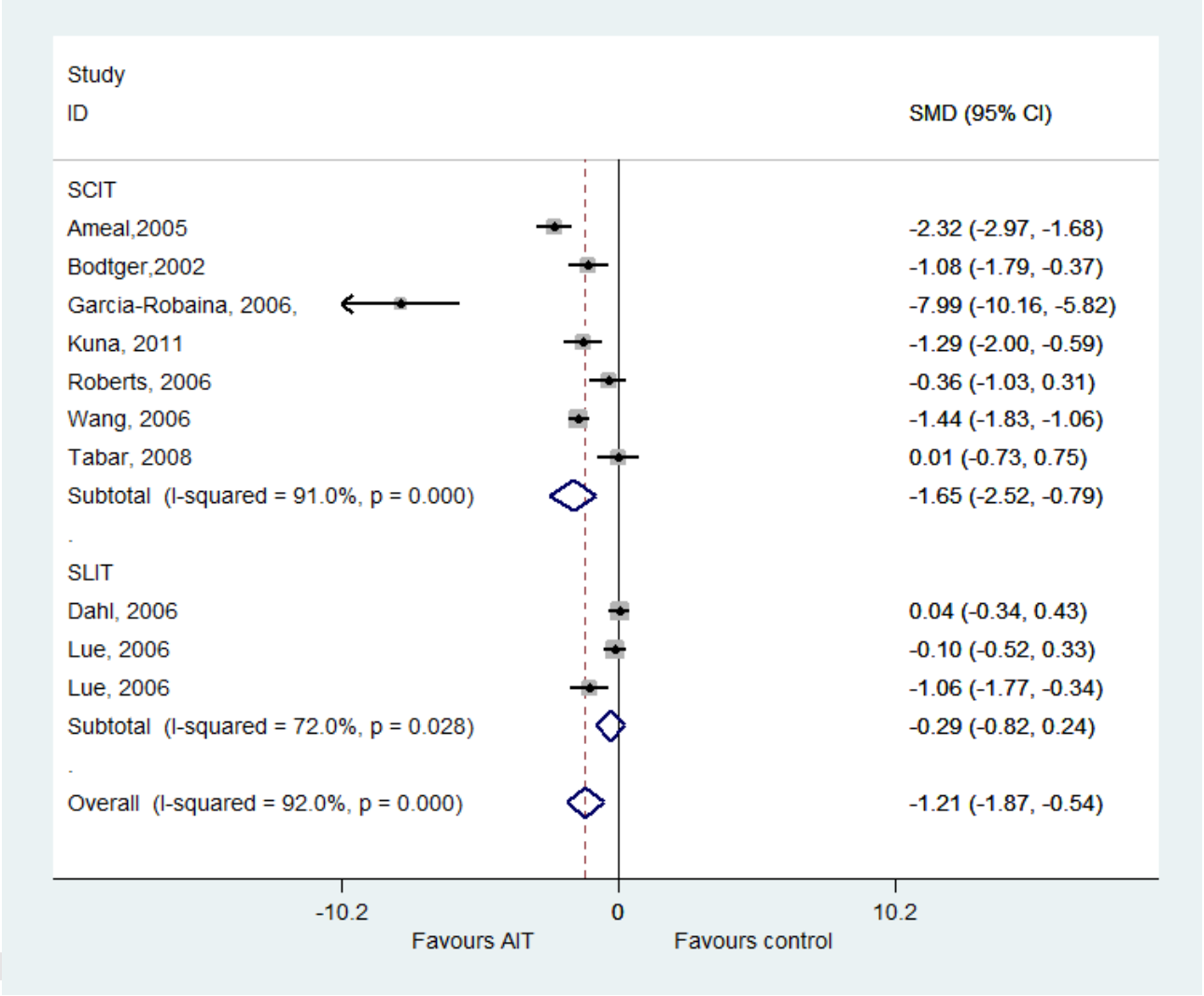
Figure 6: Meta-analysis of double-blind RCTs, comparing medication scores between AIT (SLIT and SCIT) and placebo groups in children <18 versus adults ≥18 years(random effects model)



	Het.stat.	df	P	I-squared**	Tau-squared
Adult	35.08	1	0.000	97.1%	23.2029
Children	15.79	4	0.003	74.7%	0.2244
Overall	66.41	6	0.000	91.0%	0.9722

Adult	z= 1.29	p = 0.197
Children	z= 1.96	p = 0.050
Overall	z= 2.89	p = 0.004

Figure 7: Meta-analysis of double-blind RCTs, comparing medication scores between SLIT and SCIT (random effects model)

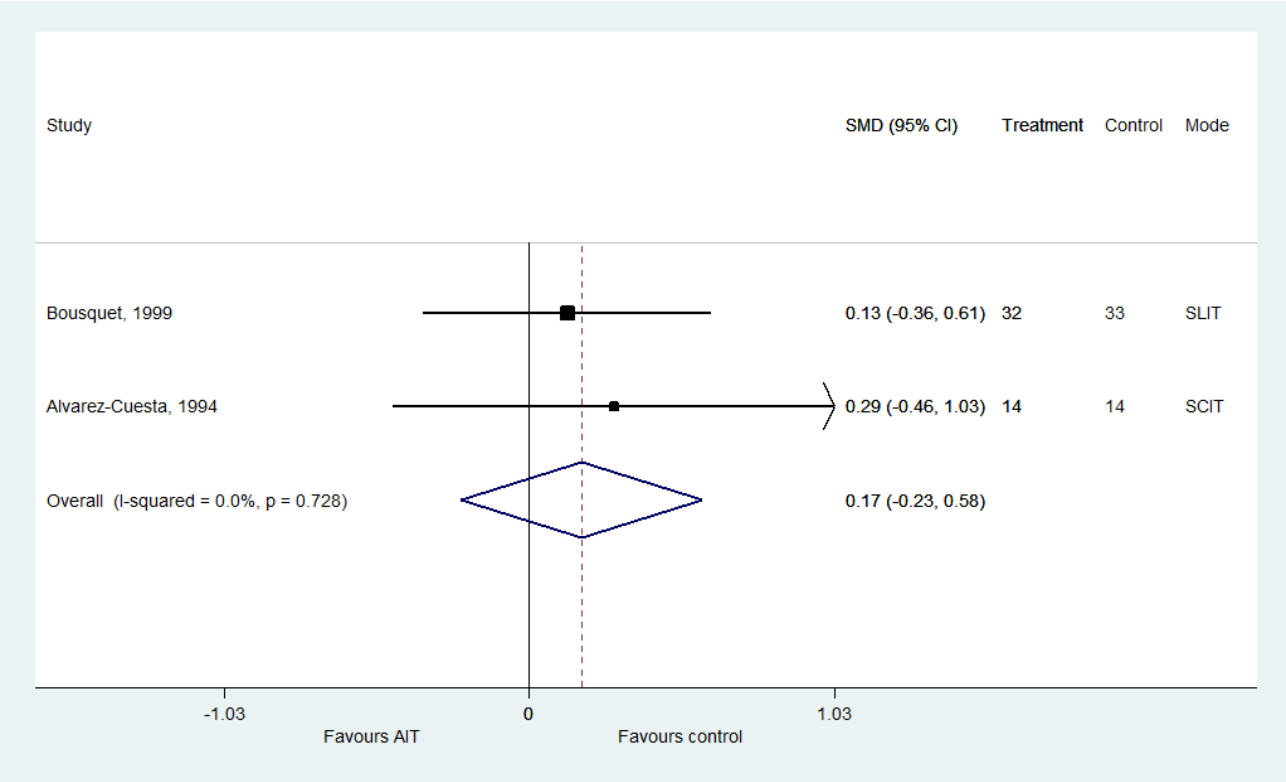


	Het. statistic	df	P	I-squared**	Tau-squared
SCIT	66.59	6	0.000	91.0%	1.1642
SLIT	7.14	2	0.028	72.0%	0.1553
Overall	112.48	9	0.000	92.0%	0.9967

Significance test(s) of ES=0

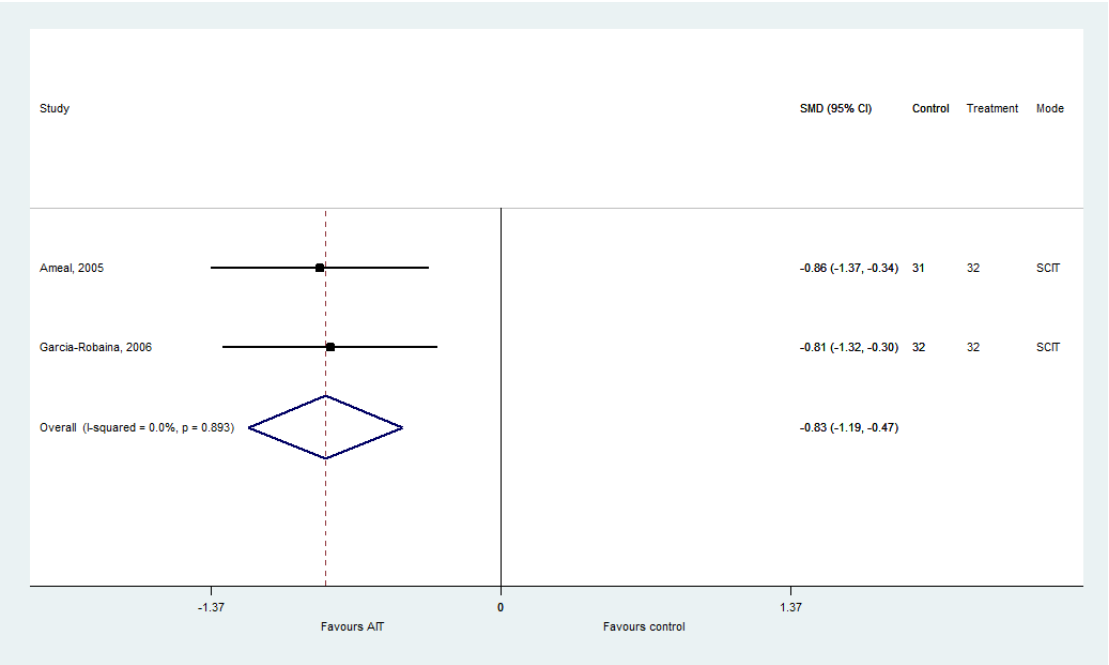
SCIT	z= 3.74	p = 0.000
SLIT	z= 1.06	p = 0.287
Overall	z= 3.56	p = 0.000

Figure 8: Meta-analysis of double-blind RCTs, comparing combined symptom medication scores between AIT (SLIT and SCIT) and placebo groups (random effects model)



Test of SMD=0 : z= 0.84 p = 0.400
Heterogeneity chi-squared = 0.12 (d.f. = 1) p = 0.728
I-squared (variation in SMD attributable to heterogeneity) = 0.0%
Estimate of between-study variance Tau-squared = 0.0000

Figure 9: Meta-analysis of double blind RCTs of AIT (SCIT and SLIT) versus placebo for asthma specific quality of life (random effects model)



Test of SMD=0 : z= 4.48 p = 0.000
Heterogeneity chi-squared = 0.02 (d.f. = 1) p = 0.893
I-squared (variation in SMD attributable to heterogeneity) = 0.0%
Estimate of between-study variance Tau-squared = 0.0000